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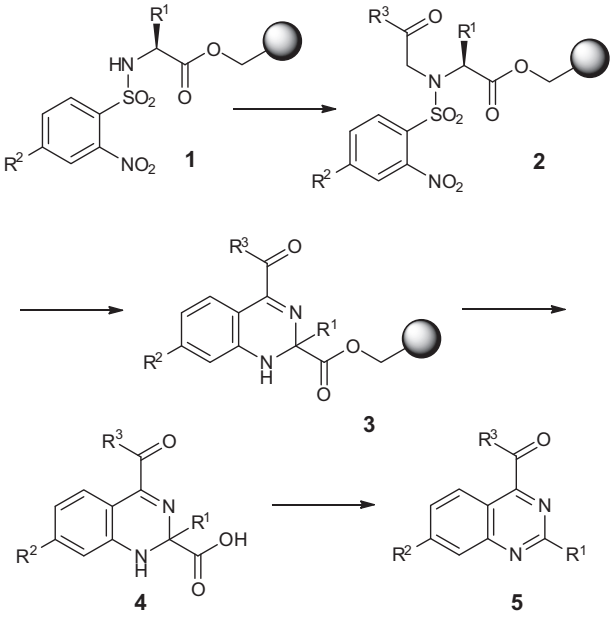
## Current literature highlights

*Traceless solid-phase synthesis of trisubstituted quinazolines*

Quinazolines, whether naturally occurring or synthetic, have long been known to have important pharmacological activities, with proven insecticidal, antibacterial, antiviral and anticancer properties. In particular, several commercial antitumour drugs such as Iressa, Tarceva and Caprelsa are potent tyrosine kinase inhibitors based on the quinazoline structure. Quinazolines when condensed with other heterocycles have also been shown to act as antitumour DNA ligands that target DNA topoisomerase.

Many reports have demonstrated efficient synthetic routes to quinazolines, but very few have addressed an efficient synthesis of 4-keto derivatives. A recent publication has described a traceless solid-phase supported method for the synthesis of 4-ketoquinazolines which is an attractive route as cleavage of products from the solid support leaves no visible functionality where the compound was covalently bound to the support [1].

The synthesis commenced with immobilisation of Fmoc-protected α-amino acids onto Wang resin support through an ester bond. Following deprotection of the amines, reaction with 4-substituted 2-nosyl chlorides gave intermediates **1**. The nosyl group activates the amine to alkylation with various substituted α-bromoketones under basic conditions to give intermediates **2**. These sulfonamides could now be reacted with DBU, and in a sequence of events that involved base-catalysed tandem C–C bond formation, cyclisation to indazole oxides, and rearrangement, the quinazolines **3** were generated. Cleavage from the resin solid support could be readily achieved by treatment with 50% trifluoroacetic acid to give **4**. At this stage there was no sign of loss of the carboxylic acid, but purification by reverse-phase HPLC in aqueous ammonium acetate buffer with acetonitrile resulted in spontaneous decarboxylation to give the final compounds **5**. The decarboxylation was monitored by LC/MS and it was found, not unexpectedly, that the rate of loss was highly dependent on the nature of substituents on the heterocyclic system.



Final products were purified by semi-preparative HPLC and isolated following freeze-drying. A number of different derivatives were prepared and crude purities were found to be in the range 52–70%. Total yields were in the range 8–56%, which were reasonable given the 7 step overall synthesis. In conclusion, this new solid-phase route provides an efficient approach to this important group of heterocyclic products.

## A summary of the papers in this month's issue

*Polymer supported synthesis*

Polymyxin B and E are used as a 'last line' therapy for infections caused by serious Gram-negative bacteria due to their highly efficient antibacterial activity and nephrotoxicity. Much research has been focused on designing polymyxin analogues by chemical synthesis in order to decrease the nephrotoxicity and simultaneously increase antibacterial activity. In a recent study, a new strategy for the solid phase total synthesis of polymyxins and their

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analogues has been described. This method was achieved by anchoring the amine side chain of Dab9 on resin followed by on-resin cyclisation. This method is more convenient and efficient, and thus maybe a good replacement for current chemical synthetic method in designing polymyxin analogues [2].

*Solution-phase synthesis*

A parallel and advantageous multi-component one pot reaction has been developed utilising a domino Aldol condensation–Michael addition–Suzuki coupling approach for a variety of 2,3-disubstituted highly functionalised quinolines. The domino reactions of 2-chloro-3-formylquinolines, acetophenones, and distinctive boronic acids, were carried out using $PdCl_2(PPh_3)_2$/tripotassium phosphate/ethanol–water system. At 80 °C they gave diversified functionalised quinolines in good yields [3].

*Scaffolds and synthons for combinatorial libraries*

No papers this month.

*Solid-phase supported reagents*

A simple, efficient, and eco-friendly method has been developed for the synthesis of 4,5-dihydropyrrolo[1,2-a]quinoxalines using sulfamic acid ($H_2NSO_3H$), a green and recyclable catalyst in water. The method employs readily available catalysts and is notable for short reaction time, operational simplicity, and high yields. The catalyst can be recovered and reused without loss of activity and more importantly, the reaction uses water as a solvent. The synthesised compounds were screened for their cytotoxic potential against two human cancer cell lines [4].

An efficient and green approach has been developed for the synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones directly from corresponding substituted aromatic and aliphatic aldehyde and anthranilamide using recyclable polymer-supported sulfonic acid catalyst under aqueous conditions. Environmental acceptability, operational simplicity, low cost, excellent functional group compatibility, and high yields are the important features of this protocol [5].

A simple and efficient procedure for the synthesis of pyrazoloisoquinoline and pyrazolopyridine derivatives by one-pot three-component condensation of aminopyrazoles, aldehydes, and cycloketones has been reported. The process takes place in water using carbonaceous material as a solid acid catalyst, and offers several advantages such as simple experimental and work-up procedures, high yield, recovery, and reusability of the metal-free solid acid heterogeneous catalyst [6].

*Novel resins, linkers and techniques*

A new method compatible with 9-fluorenylmethoxycarbonyl (Fmoc) solid phase peptide synthesis has been developed to synthesise photocaged peptides carrying the photosensitive 4-methoxy-7-nitroindoline (MNI) group on the side chain of aspartic acid (Asp) and glutamic acid (Glu). The caged building blocks, Fmoc-Asp(MNI)-OH and Fmoc-Glu(MNI)-OH, could be readily synthesised on multi-gram scale. An important advantage of the new method is that the MNI group prevents the formation of aminosuccinyl side products and pyrrolidones during Fmoc SPPS and has rapid photolysis kinetics [7].

A novel fluorous polystyrene (FPS) MR-resin has been applied to a fluorous solid-phase (FSP) reaction. The MR-FPS resin, developed previously, possessed excellent chemical resistance to acids and alkalis, and a fluorous-tagged compound was homogeneously and loosely immobilised on the resin. The synthesis of an antitumour drug, an *N*-methyl-*N*-nitrosourea conjugated 3-amino-β-carboline derivative, has been accomplished in high yield by using this new fluorous reaction system. Using only filtration, the fluorous 3-amino-β-carboline derivatives immobilised on the MR-FPS resin were easily recovered from the reaction mixtures. Subsequently, a diversity synthesis of 3-amino-9-benzyl-β-carboline derivatives has been pursued by the FSP method giving high yields [8].

*Library applications*

The dopamine D3 receptor (D3R) is a target of interest for a variety of neurological disorders including schizophrenia, Parkinson's disease, restless leg syndrome, and drug addiction. A common molecular template used in the development of D3R-selective antagonists and partial agonists incorporates a butylamide linker between two pharmacophores, a phenylpiperazine moiety and an extended aryl ring system. A recent publication describes compounds that incorporate a change to that chemical template, replacing the amide functional group in the linker chain with a 1,2,3-triazole group as a bioisostere. D3R-binding functionality of the compounds was maintained and these novel 1,2,3-triazole-containing compounds had modestly improved metabolic stability [9].

The various scaffolds containing a 1,4-dihydropyrimidine ring have been designed by considering the environment of the active site of COX-1/COX-2 and 5-LOX enzymes. A structure-based library design approach, including the focused library design and virtual screening was used to select the 1,4-dihydropyrimidine scaffold for simultaneous inhibition of both enzyme pathways. Following library enumeration and docking, ten compounds were selected for synthesis and evaluated for their COX-1, COX-2 and 5-LOX inhibiting activity [10].

The formation of a series of analogues containing a pyridine moiety in place of the natural thiazole heterocycle, found in the potent, naturally occurring HDAC inhibitor Largazole has been described. The synthetic strategy was designed modularly to access multiple inhibitors with different aryl functionalities containing both the natural depsipeptide and peptide isostere variant of the macrocycle [11].

The association of two pharmacophoric entities generates 'twin drug' or dimer derivatives, an approach recently applied for the design of a small compound library for the interaction with α4β2* nicotinic acetylcholine receptors (nAChRs). The nAChR ligand *N*,*N*-dimethyl-2-(pyridin-3-yloxy)ethan-1-amine served as one pharmacological entity and was initially kept constant as one part of the 'twin' compound. The 'twin drug' approach proved to provide compounds with high affinity and subtype selectivity for α4β2* nAChRs [12].

Human DNA topoisomerase IIα (htIIα) is a validated target for the development of novel anticancer agents. Starting from previously described 4-amino-1,3,5-triazine inhibitors of htIIα, a library of 2,4,6-trisubstituted-1,3,5-triazines was investigated to find novel inhibitors that bind to the htIIα ATP binding site. One compound was found to inhibit htIIα decatenation in a superior fashion to etoposide. 4,6-Disubstituted-1,3,5-triazin-2(1H)-ones represent the first validated monocyclic class of catalytic inhibitors that bind to the to the htIIα ATPase domain [13].

The synthesis of 2,3,5-trisubstituted 7-azaindoles as well as 2,5-disubstituted 7-azaindoles from 3,5-dihalogenated 2-aminopyridines has been outlined in a recent paper. Expertise gained in the

synthesis of azaindoles was used to assemble a few small libraries of substituted azaindoles, and some of these azaindole derivatives showed very promising biological activity against the gastrointestinal protozoal parasite *Giardia duodenalis* [14].

A facile method has been applied to the synthesis of a 15-membered library of regio- and stereoselective oxazolones-grafted spirooxindole-pyrrolidine, pyrrolizidines and pyrrolothiazoles. After screening for cytotoxic activities against a spectrum of cell-lines, one compound was identified as potent antitumour agent that induced apoptosis [15].

To develop more effective antitumour steroidal drugs a library that included twenty-two novel cytotoxic 2-alkyloxyl substituted (25R)-spirostan-1,4,6-triene-3-ones was generated. The corresponding 1,2,3-triazoles were also obtained through an abnormal monoepoxide ring-opening/elimination and 'click' reactions. After cytotoxic evaluations against HepG2, Caski and HeLa cell lines, three steroidal triazoles in this library were found to possess potent anti-proliferative effects against Caski cells with $IC_{50}$ values between 9.4 and 11.8 μM [16].

The synthesis and evaluation of a library of variably-linked ciprofloxacin dimers has been described. These structures unify and expand on the widespread use of fluoroquinolones as probes in the antibiotic literature. A dimeric analogue showed enhanced inhibition of its intracellular target (DNA gyrase), and translation to antibacterial activity in whole cells was demonstrated. A principal component analysis demonstrated that the dimers occupy a unique and privileged region of chemical space most similar to the macrolide class of antibiotics [17].

Exploring the affinity-pocket binding moiety of a 2-aminothiazole (S)-proline-amide-urea series of selective PI3Kα inhibitors using a parallel synthesis approach has led to the identification of a novel 4′,5-bisthiazole sub-series of compounds. The synthesis and optimisation of both the affinity pocket and (S)-proline amide moieties within this 4′,5-bisthiazole sub-series have been described. From this work a number of analogues were identified as potent and selective PI3Kα inhibitor *in vitro* tool compounds [18].

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## Further reading

*Papers with relevance to combinatorial chemistry or solid-phase synthesis from other journals*


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